Scientific Abstract

Approximately 130,000 new cases of colorectal carcinoma are diagnosed in the United States each year (Jessup et al., 1997). Nearly half of all patients with colorectal cancer will develop metastatic disease during the course of their illness (Meta-analysis Group, 1998). Fifteen percent of patients will have liver metastases at the time of diagnosis, and fully 60% with metastatic disease will have liver-only or liver-predominant disease (Kemeny et al., 1994). Surgical resection can offer about a third of these patients an opportunity for cure; however, the majority have unresectable lesions or lesion recurrence following resection and consequently have few treatment options (Fong et al., 1995). Systemic chemotherapy yields responses in only 15-35% of these patients, and radiotherapy is generally ineffective. Infusion of fluorinated pyrimidines (FUDR) into the liver has resulted in higher local response rates (40-60%) without a convincing improvement in overall survival. Median time to disease progression remains 6 to 9 months, while overall survival in these patients ranges from 12 to 18 months (O'Connell et al., 1998).

MediGene, Inc. is currently evaluating an oncolytic virus, NV1020, as a potential new therapy for patients with colorectal cancer that has metastasized to the liver. NV1020 is a replication-competent strain of HSV-1 that is highly attenuated for virulence. The virulence of NV1020 is highly attenuated relative to the parental strain, HSV-1 (F) due to: (i) a deletion of the internal repeat (joint region) and UL56 sequences and (ii) a 700-bp deletion that precludes expression of the UL23 (TK) and UL24 genes. Deletion of the internal repeated region of HSV-1 has been strongly associated with loss of virulence, characterized by markedly higher LD50 values compared to wild-type virus when administered intracerebrally, loss of neuroinvasiveness, impaired replication in cornea and brain, and impaired ability to establish a reactivatable latent infection (Jenkins et al., 1996, Meignier et al., 1988; Meignier et al., 1990). UL23 encodes the Thymidine Kinase (TK) protein that confers susceptibility to anti-herpes virus drug acyclovir and its analogs, but this was inactivated by removal of the 700-bp region. So that NV1020 infection can be controlled with these drugs, a functional copy of the HSV-1 TK gene was inserted into the NV1020 genome, in place of the deleted joint region. NV1020 was extensively tested in HSV-sensitive animal models prior to use in clinical trials.

MediGene has completed a phase I study, NR1-001: *A Phase I, Open-Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-tumor Activity of a Single Intrahepatic Arterial Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Subjects With Adenocarcinoma of the Colon with Metastasis to the Liver,* to investigate NV1020 as a treatment for liver metastases. Single, escalating doses of NV1020 were injected into the hepatic artery of 12 HSV-seropositive patients with colorectal carcinoma metastatic to the liver. NV1020 was well tolerated within the dose range studied (3×10^6 to 1×10^8 pfu). The most common adverse events were transient pyrexia, headache, and gastrointestinal disturbance. There were no meaningful adverse drug-related changes in various cytokines following administration of NV1020. At 1×10^8 pfu transient abnormalities in liver function tests and coagulation times suggested that this was close to the maximum tolerated dose. In 2 of the 12 patients, virus was detected in biopsies of liver tissue

three days following NV1020 administration. Carcinoembryonic antigen (CEA) levels dropped transiently after treatment with virus alone and subsequently showed marked reductions after second-line chemotherapy cycles were administered one month later. By the end of the second chemotherapy cycle, seven subjects had reached either a partial (>50% reduction) or minor (>25% reduction) objective tumor response.

All 12 patients have been followed up long-term in the extension study, NR1-002: *Long-Term Follow-Up of The Safety and Survival of Subjects With Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase 1 Dose-Escalating Study (Protocol NR1-001) Evaluating a Genetically Engineered Herpes Simplex Virus, NV1020.* The primary objectives were to assess the long-term safety and survival of the patients who received NV1020. The protocol provided periodic evaluations over a twelve-month period and then continues with intermittent telephone contact until death. No clinically meaningful or NV1020-related toxicity has been identified; follow-up of surviving patients ranges between 1 and 3 years post dosing.

MediGene plans to continue evaluating NV1020 as a potential therapy for patients with adenocarcinoma of the colon with metastasis to the liver. A newly proposed study is designed primarily to evaluate the safety of repeated administration of NV1020, prior to second line chemotherapy, in this patient population. Based on preclinical data and theoretical considerations, it is hoped that repeated administration or fractionating the dose of NV1020 might improve hepatic infectivity or improve tolerability.

The new study protocol, CT 1030, is entitled: *A Phase I/II, Open-label Study (with a Sequential Dose Escalation Stage Followed by a Randomized, Controlled Expansion of a Selected Dose Cohort), to Evaluate the Safety and Anti-tumor Effects of NV1020, Administered Repeatedly via Hepatic Artery Infusion Prior to Second Line Chemotherapy, in Patients with Colorectal Adenocarcinoma Metastatic to the Liver.* The study will evaluate the safety and tolerability of at least 3 dose levels of 4 (repeated) weekly (or biweekly in case of adverse events) injections of NV1020 administered locoregionally to the liver. Secondary study objectives include selection of an appropriate dose for later phase II studies, assessments of the anti-tumor activity of NV1020, assessment of the anti-tumor activity and progression-free survival of second line chemotherapy after NV1020 pretreatment, assessment of the immunologic activity of NV1020, evaluation of the long-term safety of NV1020, and collection of survival data on patients treated with NV1020.

The design involves a sequential, open-label cohort dose escalation of NV1020 (stage 1) followed by a randomized, controlled expansion of a selected dose cohort (stage 2). During the dose escalation stage 1, cohorts of patients (3 in each) will be treated with 4 fixed doses of NV1020 via the hepatic artery at approximately weekly intervals. Dose level will increase for successive cohorts. Each patient will be observed for a minimum of 7 days after the first NV1020 injection before the next patient in the same cohort receives NV1020 and for a minimum of 14 days before any patient in the next dose cohort receives NV1020. The study will be conducted with DSMB

oversight and with their clearance for dose cohort escalation. Additional cohorts (higher or lower half log increments) may be recommended by the DSMB, if considered necessary by them. Dose-limiting toxicity will be determined using NCI CTC criteria and an optimal dose level for further evaluation will be selected.

In stage 2, expansion of the selected dose cohort will involve 15 patients being randomized to treatment with either NV1020 + chemotherapy or chemotherapy alone in a 4:1 ratio (12 active vs. 3 no active). In each study stage, investigational treatment with NV1020 will be followed by 2 cycles of standard chemotherapy. Subjects in both stages will be periodically followed up for life.

References

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